CHAPTER 36

Hematopoietic cell transplantation

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Hematopoietic cell transplantation (HCT) is the IV infusion of hematopoietic progenitor cells designed to establish marrow and immune function in patients with a variety of acquired and inherited malignant and nonmalignant disorders. They include hematologic malignancies (eg, leukemia, lymphoma, and myeloma), nonmalignant acquired bone marrow disorders (aplastic anemia), and genetic diseases associated with abnormal hematopoiesis and function (thalassemia, sickle cell anemia, and severe combined immunodeficiency). HCT also is used in the support of patients undergoing high-dose chemotherapy for the treatment of solid tumors for which hematologic toxicity would otherwise limit drug administration (eg, breast, germ-cell, and ovarian cancers).

Types of transplantation

Since the advent of HCT in the 1960s, several different methods of transplantation have evolved. At present, the hematopoietic cells used for HCT are obtained from either bone marrow or peripheral blood. The decision to use a certain type of HCT is dictated by the patient's disease and condition and the availability of a donor. In some cases, more than one approach is possible. Table 1 summarizes the advantages and disadvantages of each stem-cell source.

Allogeneic BMT, matched related This method involves procurement of bone marrow from an HLA-identical sibling of the patient. In some cases, a partially matched sibling or family donor (one antigen mismatch) can be used for bone marrow transplantation (BMT).

Allogeneic BMT, matched unrelated Given that there are a limited number of alleles of the HLA system, typing of large numbers of individuals has led to the observation that full matches for patients exist in the general population. Tissue typing is performed on the patient's blood, and a search of the computer files of various international registries is made to determine whether a patient has a match with an unrelated individual.

Haploidentical transplantation involves the transplantation of large numbers of T-cell–depleted stem cells from a donor, usually a sibling or a parent, who is half matched to the patient. Although these are the most difficult transplantations to perform successfully, there is great interest in this approach because most patients will have a donor in their family who is at least a 50% HLA

match. Although most transplants will engraft and few patients will have significant graft-vs-host disease (GVHD), the relapse rate is high and the process of immune reconstitution is slow, with patients often having troublesome infections for a long time after transplantation.

Autologous BMT This form of transplantation entails the use of the patient's own bone marrow, which is harvested and then cryopreserved prior to administration of chemotherapy and/or high-dose radiation therapy. Following completion of therapy, the marrow cells are then thawed and reinfused into the patient to reestablish hematopoiesis.

Autologous peripheral blood stem-cell transplantation With the recognition that the marrow stem cells circulate in the peripheral blood, methods have been devised to augment the number of these cells in the patient's circulation. The blood is then collected on a cell separator and frozen, similar to autologous marrow, to be utilized after high-dose chemotherapy and/or radiation therapy. This is now the most common source of stem cells used in the autologous setting.

Syngeneic transplantation In this form of transplantation, marrow or peripheral blood stem cells are procured from an individual who is a genetic identical twin to the patient.

Donor leukocyte infusion This method involves the infusion of mononuclear cells from the marrow donor into the recipient to treat relapse after transplantation. The cells can mediate an antitumor effect, known as a graft-vs-tumor effect (often in association with concomitant GVHD), and can achieve remission of the malignancy.

Nonmyeloablative or reduced-intensity transplantation This approach uses lower doses of chemotherapy, with or without total-body irradiation (TBI) and immunosuppression, to facilitate engraftment of donor stem cells. Donor stem cells obtained from either the peripheral blood or marrow are then infused into the patient, leading to hematopoietic engraftment. The major therapeutic effect that results from this type of transplantation is a graft-vs-tumor effect, as the nonmyeloablative regimen has little antitumor efficacy. Some disorders such as chronic myelogenous leukemia (CML), acute myelogenous leukemia (AML), low-grade lymphoma, and multiple myeloma are particularly sensitive to this approach. This type of transplant allows older patients to undergo the procedure, as the transplant-related mortality is greatly reduced with this approach.

Cord blood transplantation The blood in the umbilical cord of newborn babies contains large numbers of stem cells, which have been shown to be capable of long-term engraftment in children and some adults after transplantation. Similar to unrelated-donor registries, cord blood banks have been developed to store cord blood cells that can be utilized for unrelated-donor transplantation. Given the immunologic immaturity of cord blood cells, these transplants can be accomplished even when there are disparities (mismatching) in the HLA typing between the donor and recipient. Cord blood transplants are generally used in situations where an adult unrelated donor cannot be identified through the international registries.

TABLE 1: Stem-cell sources for allogeneic BMT

Type	Advantages	Disadvantages
Allogeneic		
Sibling donor 6/6 HLA match or 5/6	Match able to be identified rapidly (2 weeks)	GVHD (25%-40%) for non–T-cell-depleted marrow grafts
	Low rate of graft rejection (2%-5%)	Only 30% of patients will have sibling donor
Matched unrelated donor	Extends donor availability (60%-70% of patients will have potential match)	Takes time to find donor (6 weeks to > 6 months)
	Higher graft-vs-tumor effect	Higher graft failure rates (5%-10%)
		Higher GVHD rates (50%-60%)
Umbilical cord donor	Lesser degrees of match can be used	Limited number of cells (reduced applicability to large recipient)
		Slower engraftment
	Much lower rate of GVHD (10%-20%) despite one and two antigen mismatches	Higher rate of graft failure (10%)
		No chance for second infusion for graft failure or DLI for relapse
Haploidentical family donor	Almost all patients have a sibling, parent, or child who is haploidentical. These donors can be used if patients have relapsed or there is refractory disease and no better donor has has been identified	Needs much more profound immunosuppression (T-cell depletion of donor product included) to achieve engraftment
		High risk of infectious complications
		Graft failure rate of 10%-15%
Syngeneic Identical twin	No need for immunosuppression	No graft-vs-tumor effect
	No GVHD	

DLI = donor lymphocyte infusion; GVHD = graft-vs-host disease

Allogeneic transplantation

HLA typing

Finding a related donor As noted previously, matched related allogeneic BMT involves a donor who is an HLA-matched sibling of the recipient. The formula for calculating the chances of a particular person having an HLA-matched sibling is $1 - (0.75)^N$, where N denotes the number of potential sibling donors. In general, a patient with one sibling has a 25% chance of having a match. The

average American family size usually limits the success of finding a family donor to approximately 30% of patients.

HLA typing is performed on blood samples obtained from the patient and potential donor. Serologic methods have been used to detect the identity of the class I and II antigens; molecular methods are now utilized for more refined matching of both classes. A match is noted when the major class I antigens (A and B loci), as well as class II antigens (DR), are the same as those of the donor. Each sibling receives one set of antigens (A, B, DR) from each parent (chromosome 6). Genotypic identity can be confirmed by testing the parents and determining the inheritance of each set of antigens.

Finding an unrelated donor In cases in which the patient needs an allogeneic transplant and a donor cannot be found within the family, the identification of a matched-unrelated donor is accomplished by searching the computer files of the National Marrow Donor Program, as well as other international registries. As there are multiple alleles of any given HLA locus, serologic identity does not necessarily imply genotypic identity, such as is the case among sibling donor-recipient pairs. The development of oligonucleotide probes has greatly increased the precision of HLA typing and has allowed for more specific selection of bone marrow donors by matching molecular alleles of the class I and II antigens.

Advantages and disadvantages

The major advantages of an allogeneic graft include the absence of malignant cells contaminating the graft; the potential for an immunologic anticancer graft-vs-tumor effect; and the ability to treat malignant and nonmalignant disorders of the bone marrow, including genetic and immunologic diseases.

The disadvantages of an allogeneic transplant include the difficulty in finding an appropriate HLA-matched donor and the development of GVHD after BMT, which contributes to the morbidity and mortality of the procedure.

Autologous transplantation

Advantages and disadvantages

In autologous transplantation, the reinfused stem cells come from either the patient's own bone marrow or peripheral blood. These cells do not cause GVHD, and, thus, autologous transplantation is associated with less morbidity and mortality than allogeneic BMT and increases the number of patients who can undergo the procedure, as well as the upper age limit.

The disadvantages of autologous BMT include the likelihood of tumor cell contamination within the graft in many diseases, which can cause relapse; the lack of a significant therapeutic graft-vs-tumor effect; and the limited ability to use autologous stem cells in the treatment of patients not in remission or with inherited nonmalignant lymphohematopoietic diseases. Table 2 summarizes the advantages and disadvantages of these two approaches.

TABLE 2: Comparison of allogeneic vs autologous stem-cell transplantation

Allogeneic
Advantages
No tumor contamination of the graft and no prior marrow injury from chemotherapy (less risk of later myelodysplasia)
Graft-vs-tumor effect
Can be used for patients with marrow involvement by tumor or with bone marrow dysfunction, such as aplastic anemia, hemoglobinopathies, or prior pelvic irradiation
Disadvantages
Dose-intensive regimen limited by toxicity (usually limited to patients < age 55)
Takes time to identify donor if no sibling donor available/limited availability of donor for some ethnic groups
Higher early treatment-related mortality from graft-vs-host disease and infectious complications (20%-40% depending on age and donor source)
Autologous
Advantages
No need to identify donor if peripheral blood marrow uninvolved by tumor at time of collection
No immunosuppression = less risk of infections
No graft-vs-host disease
Dose-intensive therapy can be used for older patients (usually up to age 70)
Low early treatment-related mortality (2%-5%)
Disadvantages
Not feasible if peripheral blood stem cells/marrow involved
Possible marrow injury leading to late myelodysplasia (either from prior chemotherapy or transplant regimen)
No graft-vs-tumor effect
Not all patients can be mobilized to give adequate cell doses for reconstitution

Modifications of the stem-cell graft

The disadvantages of both allogeneic and autologous transplantation have led to the development of modifications of the stem-cell graft.

Removing T cells from donor marrow With regard to allogeneic BMT, it is known that contaminating T cells from the donor mediate the onset and persistence of acute and chronic GVHD. T cells have been removed from the donor marrow in an attempt to prevent the development of severe GVHD. However, this approach has increased the incidence of both graft rejection and relapse of malignancy. Some investigators are exploring planned add-back of donor T cells after hematopoietic recovery to help prevent relapse.

Primed peripheral blood stem cells from marrow donors have reduced transplant-related complications without a substantial increase in GVHD. Thus far, the data show that this approach induces more rapid engraftment. Some studies have reported an increase in chronic GVHD.

Eliminating tumor cells from autologous grafts Although autologous peripheral blood stem-cell transplantation has led to more rapid restoration of hematopoiesis, it is associated with a higher relapse rate than allogeneic BMT. Attempts to deplete the autologous graft of tumor cells have included in vitro purging with monoclonal antibodies and/or chemotherapeutic agents and the enrichment of stem cells over various separation columns.

Post-transplantation immunomodulation For patients undergoing autologous transplantation, several post-transplantation immunomodulating strategies and interleukin-2 (IL-2, aldesleukin [Proleukin]) are being tested. The plan is to determine whether they will decrease relapse by augmenting immunologic antitumor responses following transplantation. In some diseases such as myeloma, post-transplant treatment with medication such as dexamethasone, and with thalidomide (Thalomid) helps prolong remission.

Collection of the graft

Allogeneic bone marrow cells Current techniques for harvesting bone marrow involve repeated aspirations from the posterior iliac crests, designed to obtain adequate numbers of cells that can lead to hematopoiesis. While the donor is under general or spinal anesthesia, between 1 to 3×10^8 cells/kg of the recipient's body weight are procured. The procedure has no long-term side effects and poses little risk if care is taken to ensure that the donor has no confounding medical conditions. In most cases of ABO incompatibility, the marrow can be treated to remove RBCs to prevent lysis after infusion.

Although busulfan-based regimens are the most commonly used worldwide for allogeneic transplantation, the oral administration of the drug leads to unpredictable absorption, which has been correlated with relapse (low absorption) and increased toxicity (increased absorption). Recent studies with an intravenous formulation of the drug have shown much more predictable pharmacokinetics, less toxicity, and good survival when utilized in the transplantation regimen.

Autologous peripheral stem cells Collection of circulating peripheral blood progenitor cells is performed via an apheresis technique. Although this procedure can be accomplished in an individual with a baseline blood count, the number of cells and the efficiency of collection are increased if the cells are procured during WBC recovery following chemotherapy or after the administration of hematopoietic growth factors.

The most effective strategy appears to be the collection of cells after both chemotherapy and administration of growth factors. In most circumstances, adequate numbers of cells can be collected utilizing granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) or granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim [Leukine]) to prime the patient prior to one to three apheresis procedures.

Currently, the adequacy of the number of hematopoietic stem cells is assessed by determining the number of cells that have the CD34 antigen (stem-cell) marker. Usually, a minimum of 2×10^6 CD34 cells/kg of body weight is required to ensure engraftment.

The use of autologous stem cells continues to undergo refinement. Approaches under study include ex vivo expansion to augment the number of progenitor cells, as well as techniques that separate hematopoietic cells from any potential contaminating tumor cells. In addition, hematopoietic stem cells are the usual targets of marrow-based gene therapy utilizing viral vectors for transduction of cells prior to cryopreservation.

Indications for transplantation

The expanded methods of stem-cell transplantation have complicated the choice for patients and their physicians among the different types of transplantation in some instances. Therefore, the decision requires evaluation of the patient and the disease involved. In general, for disorders that require replacement of an abnormally functioning hematopoietic system, such as thalassemia and aplastic anemia, an allogeneic transplantation is performed. However, as genetic therapy for hematopoietic stem cells becomes more of a reality, even patients with these diseases may be candidates for autologous transplantation after gene modification (adenosine deaminase deficiency, chronic granulomatous disease).

Hematologic malignancies The most common use of allogeneic BMT has been for the eradication of hematologic malignancies, such as leukemia and non-Hodgkin's lymphoma. For some disorders (aplastic anemia, myelodysplasia, leukemia in relapse, and CML), allogeneic transplantation is the only significant therapeutic option, whereas for other diseases (AML in remission, lymphoma, Hodgkin's disease, and multiple myeloma), either autologous or allogeneic marrow grafting may be possible.

Nonmyeloablative or reduced-intensity transplantation approaches are being studied worldwide, which has facilitated transplantation for many people who otherwise would not have been candidates due to concomitant medical problems or older age. The results indicate that malignancies that are not rapidly progressive are the most responsive. Thus, patients with low-grade lymphoma, AML, myeloma, myelodysplasia, and CML are probably good candidates for this type of allogeneic transplantation, whereas those with advanced disease such as leukemia in relapse or high-grade lymphoma benefit less, as the allogeneic antitumor effect requires time to develop and achieve remission of the disease. Table 3 shows the relative sensitivity of different hematologic malignancies to a graft-vs-malignancy effect that could be mediated by a nonmyeloablative transplant.

Solid tumors In general, only autologous transplantation is utilized for some solid tumors, such as breast, germ-cell, and ovarian cancers. Studies and longer follow-up of recently completed trials continue to determine whether there is a

TABLE 3: Disease sensitivity to a graft-vs-malignancy effect

Most sensitive
Chronic myelogenous leukemia
Low-grade lymphoma
Mantle cell lymphoma
Chronic lymphocytic leukemia
Intermediate
Acute myelogenous leukemia
Intermediate-grade lymphoma
Multiple myeloma
Renal cell carcinoma
Least sensitive
Acute lymphoblastic leukemia
High-grade lymphoma
Hodgkin's disease(?)

benefit in the use of transplant-based approaches in the treatment of high-risk (stages II, IIIA, IIIB) and metastatic (stage IV) breast cancer.

Timing of transplantation

The Goldie-Coldman model proposes that the probability that a tumor contains treatment-resistant cells is a function of its size and inherent mutation rate. This finding suggests that the likelihood of cure is greatest when marrow transplantation is performed early in the natural history of an inherently chemosensitive tumor. Studies to date indicate that patients undergoing transplantation late in their disease course have inferior disease-free survival, compared with those who undergo transplantation early.

Phases of transplantation

PREPARATIVE PHASE

In the first phase of marrow transplantation, the preparative phase, patients receive high-dose chemotherapy and/or radiation therapy (sometimes referred to as a conditioning regimen).

Allogeneic transplantation The conditioning regimen used in the allogeneic setting has both a therapeutic component designed to eliminate tumor cells and an immunosuppressive component to prevent host immune responses from rejecting the transplanted donor graft. The doses of radiation therapy and chemotherapy employed take advantage of the steep dose-response curve that exists for many malignancies. The doses have been established based on the limitations of other nonhematopoietic organs, such as the liver and lungs.

TABLE 4: Acute and long-term toxicities of common preparative agents used for BMT

Agent	Acute toxicity	Long-term toxicity
Total-body irradiation	Nausea, vomiting, enteritis, mucositis	Cataracts, sterility, pneumonitis, myelodysplasia
Cyclophosphamide	Nausea, vomiting, hemorrhagic cystitis, cardiac toxicity	Sterility, leukemia
Etoposide	Skin rash, hypotension, acidosis, mucositis	Leukemia
Carmustine (BiCNU)	Seizures, nausea, vomiting, headaches	Interstitial pneumonitis
Busulfan	Seizures, nausea, vomiting, veno-occlusive disease	Alopecia, pulmonary fibrosis
Cisplatin	Renal impairment, hearing loss, tinnitus	Hearing loss, tinnitus, neuropathy
Thiotepa	Nausea, vomiting, CNS changes, veno-occlusive disease	—
Paclitaxel	Allergic reactions	Neuropathy
Fludarabine	Hemolytic anemia, CNS changes	Prolonged immune suppression, EBV-related lympho-proliferative disorder
Melphalan	Nausea, pulmonary	Peripheral neuropathy

EBV = Epstein-Barr virus

Typically, preparative regimens for allogeneic BMT consist of TBI and/or chemotherapeutic agents (cyclophosphamide [Cytoxan, Neosar], busulfan [Busulfex, Myleran], and etoposide). The most commonly used regimens are (1) TBI (1,200-1,400 cGy administered in multiple fractions over a period of days) and cyclophosphamide (60 mg/kg for 2 days); (2) fractionated TBI and etoposide (60 mg/kg); and (3) busulfan (16 mg/kg over 4 days) and cyclophosphamide (60 mg/kg for 2 days).

Autologous transplantation For patients undergoing autologous transplantation, stem cells are reinfused following high-dose therapy to reestablish hematopoiesis as rapidly as possible. The regimens used for autologous BMT depend on the disease being treated.

Toxicities of preparative regimens The acute toxicities of irradiation and chemotherapy include nausea and vomiting, which can be managed by prophylactic use of antiemetics, particularly serotonin antagonists. Busulfan can cause seizures; prophylactic phenytoin is effective in preventing this complication. Both cyclophosphamide and etoposide require forced hydration to reduce toxicities. Table 4 lists the acute and long-term toxicities of the major agents used in BMT preparative regimens.

TRANSPLANT PHASE

After completion of the preparative regimen, there is a day or more wait before reinfusion of marrow or peripheral blood stem cells. This delay allows for elimination of any active drug metabolites so that the reinfused cells are not injured by any remaining drug.

Minimal toxicities are associated with the infusion. They include headache, nausea, and dizziness. Dizziness is related more to the cryoprotectant dimethyl sulfoxide (DMSO) used to store cells from most patients undergoing autologous transplantation.

SUPPORTIVE CARE PHASE

Following administration of the preparative regimen and during and after marrow transplantation, all patients require strict attention to infectious disease-related complications secondary to neutropenia. The duration of neutropenia following transplantation increases the risk of complicating infections. Patients undergoing full allogeneic transplantation usually require more stringent isolation, whereas patients undergoing autologous transplantation need less rigorous protection. With the availability of more effective antiemetics (eg, ondansetron [Zofran] and granisetron [Kytril]), portions of the transplantation can now be performed in the outpatient setting.

Following allogeneic transplantation, various complications may develop that require treatment. For some complications, prophylactic measures can be instituted to prevent their occurrence.

Neutropenic sepsis

Nearly all patients undergoing transplantation will develop fever, often with positive blood cultures, within 7 days of becoming neutropenic. Sepsis usually is caused by enteric bacteria or those found on the skin, and antibiotic choices are based on initial assessment and the results of blood cultures. The antibiotics chosen are continued until the neutrophil count begins to rise (> 500 k/μL neutrophils). Most patients undergoing allogeneic transplantation usually receive bowel decontamination (eg, with a fluoroquinolone, such as levofloxacin [Levaquin], 500 mg/d PO) in the post-transplantation phase to reduce the risk of serious infection during neutropenia.

Prevention of fungal infections For patients who are expected to have prolonged neutropenia, various methods of antifungal prophylaxis are used, including low-dose IV amphotericin B (Fungizone; 5-10 mg/d), IV or PO fluconazole (Diflucan; 200 mg bid), or voriconazole (Vfend; 200 mg IV or PO bid). For patients who continue to have a high fever despite systemic antibiotics, the dose of IV amphotericin B is usually increased to 25-30 mg/d, depending on renal tolerance, and is continued until the neutrophil count recovers. The use of liposomal amphotericin B (AmBisome or Abelcet) formulations has improved safety and lowered toxicity of antifungal therapy and is particularly worthwhile in patients with renal compromise.

Mucositis, nausea, and anorexia

Regimen-related toxicity often results in severe oral mucositis, nausea, and anorexia. Patients often require supplemental parenteral nutrition to maintain adequate caloric intake during this period. Because of the mucositis, enteral feedings are usually not employed, and total parenteral nutrition is maintained until patients are able to eat. Studies are exploring novel agents that could prevent severe mucositis or accelerate healing with keratinocyte growth factor (KGF), which has been shown recently to decrease this complication following TBI-based autologous transplant regimens.

Oral HSV reactivation

Nearly all patients who are seropositive for herpes simplex virus (HSV) will have a reactivation of the virus, which can accentuate the pain and oral discomfort following BMT. To prevent this problem, most transplant programs utilize acyclovir (Zovirax) at a dose of 250 mg/m^2 tid during the neutropenic phase.

Transfusion

All patients will require both RBCs and platelets in proportion to the duration of the pancytopenia. Platelets are kept over 10,000-20,000/μL because of complicating bleeding from mucositis, although, in some instances, a lower threshold is feasible. Patients no longer receive granulocyte transfusions unless they have uncontrolled sepsis with positive blood cultures. For patients who are negative for cytomegalovirus (CMV) and who have a CMV-negative donor, CMV-negative cell support is generally provided (see section on "CMV infection").

All blood products are irradiated to prevent engraftment of lymphoid cells and are often filtered to reduce CMV or alloimmunization and febrile reactions. Most patients receive single-donor platelet pheresis products, which may need to be HLA-matched if patients show evidence of refractoriness to the transfusion (ie, if platelet levels fail to rise after transfusion).

Sinusoidal obstruction syndrome (veno-occlusive disease)

In the first few weeks after BMT, sinusoidal obstruction syndrome, characterized by hepatomegaly, jaundice, and fluid retention, develops in 5%-20% of patients. It is caused by damaged endothelial cells, sinusoids, and hepatocytes and is related to the intensity of the cytoreductive therapeutic regimen.

The diagnosis of sinusoidal obstruction syndrome is usually made on clinical grounds, based on the occurrence (usually within 8-10 days after starting the cytoreductive regimen) of the triad of hepatomegaly, weight gain, and jaundice. Patients also exhibit renal sodium retention, and prognosis is related to the degree of liver and kidney dysfunction and the level of bilirubin. The use of regimens that contain busulfan has been associated with the highest incidence of veno-occlusive disease, which has decreased with targeted oral or intravenous busulfan dosing.

TABLE 5: Clinical classification of acute GVHD according to organ injury

Stage Key	0	1	2	3	4
Skin	No rash	Maculopapular rash, less than 25% of body surface	Maculopapular rash, 25%-50% of body surface	Rash on greater than 50% of body surface or generalized erythroderma	Generalized or erythroderma with bullous formation and/or desquamation
Lower GI (diarrhea)	Less than or equal to 500 mL/d or less than 280 mL/m^2	Greater than 500 but ≤ 1,000 mL/d or 280 to 555 mL/m^2	Greater than 1,000 but ≤ 1,500 mL/d or 556 to 833 mL/m^2	> 1,500 mL/d or > 833 mL/m^2	Severe abdominal pain with or without ileus, or stool with frank blood or melena
Upper GI	No protracted nausea and vomiting	Persistent nausea, vomiting, or anorexia plus biopsy showing a GVHD of the stomach or duodenum			
Liver (total bilirubin)	Less than 2.0 mg/dL	2.0-3.0 mg/dL	3.1-6.0 mg/dL	6.1-15.0 mg/dL	> 15 mg/dL

Overall clinical grading of severity of acute GVHD–1994 Keystone Consensus Criteria

Grade	Skin		Liver		Gut		Karnofsky performance scale (KPS)
I	1-2	&	0	&	0		
II	3	or	1	or	1		
III	0-4	or	2-3	or	2-4		
IV	4	or	4	or	0-4	or	KPS score ≤ 30% or decrease ≥ 40% from baseline KPS score

GVHD = graft-vs-host disease

TABLE 6: Prophylaxis of acute graft-versus-host disease

Day	Cyclosporine	Methotrexate
–2	5 mg/kg IV daily	
+1	5 mg/kg IV daily	15 mg/m^2 IV single dose
+3	5 mg/kg IV daily	10 mg/m^2 IV single dose
+4	3 mg/kg IV daily	
+6	3 mg/kg IV daily	10 mg/m^2 IV single dose
+11	3 mg/kg IV daily	10 mg/m^2 IV single dose
+15	2.75 mg/kg IV daily	
+36	10 mg/kg PO daily	
+84	8 mg/kg PO daily	
+98	6 mg/kg PO daily	
+120	4 mg/kg PO daily	
+180	off	

Treatment Once veno-occlusive disease has occurred, treatment is primarily supportive, consisting of careful management of fluid overload, kidney dysfunction, and other attendant complications. In few cases, the early use of thrombolytic agents can reverse established veno-occlusive disease. Defibrotide is now being tested in phase II trials as an agent that can help reverse the syndrome.

Acute GVHD

GVHD is a clinical syndrome that results from the infusion of immunocompetent lymphocytes accompanying the marrow graft that are capable of recognizing minor HLA-related antigens in the host and initiating an immunologic reaction. This syndrome may arise after allogeneic transplantation or rarely after transfusion of cellular blood products in patients who are immunodeficient and share HLA loci that allow engraftment of transfused cells. For unknown reasons, the primary organs affected by acute GVHD are the skin, liver, and GI tract.

The syndrome usually occurs within 15-60 days after transplantation and can vary in severity. Table 5 shows a commonly used grading system for GVHD. This system has both therapeutic and prognostic importance.

Prophylaxis All patients undergoing non–T-cell-depleted transplantation require some form of GVHD prophylaxis. The most common regimens involve a combination of methotrexate and cyclosporine or tacrolimus [Prograf] or cyclosporine and prednisone. The combination of tacrolimus and sirolimus (Rapamune) has been studied and appears to be an effective approach for the prevention of GVHD. Cyclosporine, in the absence of GVHD, is tapered over

6-12 months after BMT. Table 6 shows a common regimen used to prevent GVHD after an allogeneic sibling transplantation.

Treatment Despite prophylaxis, many allogeneic transplant recipients still develop some degree of GVHD and require increasing doses of prednisone (1-2 mg/kg/d). For patients who do not respond to steroids, antithymocyte globulin (Atgam; 10 mg/kg/d for 5-10 days) has been used. Daclizumab (Zenapax; 1 mg/kg on days 1, 4, 8, 15, and 22) and pentostatin (Nipent) are likely more effective agents than antithymocyte globulin.

Chronic GVHD

Chronic GVHD may occur within 3-6 months in patients who have undergone allogeneic marrow transplantation. It is often preceded by acute GVHD, which may or may not have resolved. Although chronic GVHD is also related to infusion of T cells with the marrow graft, it resembles other autoimmune connective tissue diseases, such as scleroderma, Sjögren's syndrome, biliary cirrhosis, and bronchiolitis obliterans. Patients with chronic GVHD often have accompanying cytopenias and immune deficiency.

Treatment Chronic GVHD is generally treated with prolonged courses of steroids, cyclosporine, tacrolimus, and, occasionally, azathioprine and other modalities, such as psoralen-ultraviolet A light (PUVA) for skin and mouth GVHD. Thalidomide, mycophenolate mofetil (CellCept), sirolimus, and photopheresis have also been employed, with varying response rates. Like that for acute GVHD, the prognosis for chronic GVHD is related to the extent of organ compromise and response to treatment.

GVHD and relapse Although, in general, GVHD has contributed to significant morbidity and mortality in patients undergoing allogeneic marrow transplantation, it is also associated with reduced relapse rates, primarily in patients with hematologic malignancies.

Late infections

Late infections after BMT are caused by impaired cellular and humoral immunity. The most common late pathogens include *Pneumocystis carinii*, varicella zoster, and encapsulated bacteria.

***Pneumocystis* prophylaxis** All patients undergoing allogeneic transplantation require prophylaxis against *P carinii*. This can be accomplished with one double-strength trimethoprim-sulfamethoxazole tablet bid twice a week once hematopoiesis has been restored. Alternatively, inhaled pentamidine (NebuPent, Pentam 300) has been utilized, but due to failures with this approach, it is not preferred.

Treatment of herpes zoster Approximately 40% of patients will develop herpes zoster (either dermatomal or disseminated), which is often treated with oral or IV acyclovir. A patient may complain of severe localized pain for several days before the rash develops. The use of valacyclovir (Valtrex) for 1 year after BMT can reduce the risk of reactivation of herpes zoster after allogeneic BMT.

Bacterial prophylaxis Many patients with chronic GVHD develop an accompanying severe immunodeficiency syndrome that leaves them susceptible to infection with encapsulated bacteria, primarily in the sinuses and lungs. In some cases, prolonged prophylaxis with trimethoprim-sulfamethoxazole or penicillin is necessary, as well as immunoglobulin replacement.

CMV infection

Historically, CMV interstitial pneumonia has been responsible for approximately 15%-20% of patient deaths following allogeneic marrow transplantation. CMV pneumonia occurs 7-10 weeks after BMT and is due to reactivation of latent CMV or is acquired from donor marrow or transfusions. Active CMV infection, GVHD, and the inability to develop a virus-specific immune response that limits viral infection are risk factors for CMV pneumonia.

Diagnosis Infection is diagnosed by the combination of an abnormal chest x-ray, hypoxemia, and the detection of CMV in bronchoalveolar lavage or lung biopsy specimens, as well as the absence of other pathogens.

Treatment The only consistent treatment has been the combination of ganciclovir, 5 mg/kg bid for 3 weeks, and IV immunoglobulin, given every other day. Although the reason for the synergy between these agents is unclear, neither one alone is effective in reversing pneumonia once it has developed.

Prevention in CMV-seronegative patients The most successful means of preventing CMV infection in CMV-seronegative patients who have a seronegative donor is to limit their exposure to the virus by providing CMV-negative blood and platelet support. As most patients who undergo marrow transplantation are CMV-seropositive, this strategy has limited application. However, the presence of leukocytes in blood products increases the transmission of CMV. Thus, the use of CMV-seronegative blood products in CMV-seronegative recipients decreases the incidence of primary CMV infection. Also, CMV status should be determined in all patients prior to BMT to plan for post-transplantation transfusion strategies.

Prevention in CMV-seropositive patients The most effective strategy for preventing reactivation of CMV infection in patients who are CMV-seropositive is the preemptive use of ganciclovir, either prophylactically in all CMV-seropositive patients or at the first sign of CMV after transplantation (as indicated by blood culture, shell viral culture, or antigen or polymerase chain reaction [PCR] detection of the virus). The timing and duration of prophylaxis are somewhat controversial.

Ganciclovir has been the most effective agent for both strategies, as it significantly reduces both viral reactivation and associated disease. However, if one waits until after viral reactivation to initiate ganciclovir therapy, there are some patients who will not benefit from a prophylactic strategy, namely those in whom reactivation occurs simultaneously with disease. Ganciclovir has many side effects, including neutropenia and elevated creatinine levels, and thus exposes a large number of patients to potential toxicity.

The required duration of ganciclovir treatment is also unclear, but it would appear that several weeks is necessary to protect the patient from viral reactivation and the development of pneumonitis within the first 3 months after BMT. Monitoring for CMV of all patients after completion of antiviral therapy is necessary, as some patients, particularly those with GVHD are at risk for infection due to an inadequate immune response against CMV. Some patients have developed late CMV pneumonia after drug discontinuation that is probably related to ganciclovir inhibition of the development of CMV-specific cytolytic T cells. Nevertheless, the use of ganciclovir has reduced the problems related to CMV pneumonia and should be a part of every management strategy for preventing complications following allogeneic transplantation.

Other post-transplantation therapies

Growth factors have found their most significant use in the acceleration of hematopoietic recovery after autologous reinfusion of stem cells. Clinical trials in allogeneic transplantation have not yet shown an advantage to their use, probably due to the immunosuppressive medications such as methotrexate used to prevent GVHD. Studies do support the use of G-CSF or GM-CSF after autologous marrow transplantation, although the impact of these growth factors on acceleration of hematopoietic recovery, beyond that achieved with the use of primed autologous stem cells, is still under investigation.

Erythropoietin (Epogen, Procrit) or darbepoetin alfa (Aranesp) is sometimes used effectively in patients who have persistent anemia after transplantation.

Management of relapse

Despite the intensity of the preparative regimen, some patients relapse after allogeneic BMT. For patients with CML, withdrawal of immunosuppression to allow for an augmented graft-vs-tumor effect sometimes leads to remission. Other patients with CML may respond to post-transplantation interferon, which appears to be a useful approach. Intriguingly, infusion of donor lymphoid cells in patients with CML is an effective means of inducing hematologic and cytogenetic responses in those who have relapsed after transplantation; this approach has led to complete and durable remissions.

Some patients with AML have responded to either infusion of donor stem cells or the combination of chemotherapy and donor stem cells. Patients with acute lymphoblastic leukemia have had the lowest response rate to this strategy. Patients who develop myelodysplasia after autologous transplantation can sometimes be treated with an allogeneic transplant to restore normal hematopoiesis.

Second malignancy after hematopoietic cell transplantation

Patients undergoing transplantation are at risk for developing a second cancer. For those undergoing autologous transplantation, particularly for treatment of lymphoma and Hodgkin's lymphoma, the most common cancer is myelodysplasia/AML, which occurs in up to 10% of patients, usually within 3 to 7 years after transplantation.

Risk factors for the development of myelodysplasia/AML after transplantation include the number of prior chemotherapy and radiation therapy treatments, specific drugs such as alkylating agents or topoisomerase inhibitors, difficulty in mobilizing stem cells, persistent cytopenias after transplantation, and use of TBI in the transplant preparative regimen. All patients should undergo cytogenetic screening of the marrow prior to stem cell collection and should be followed for this complication after recovery from transplantation.

Patients undergoing either autologous and allogeneic transplantation are also at risk for the development of solid tumors, up to 20 years after transplantation. The risk is greater in patients receiving an allogeneic transplant. The most common tumors are related to the skin, but both common (breast, lung, and colon) and less common (sarcoma) tumors have been seen. As part of their long-term follow-up, all patients require screening for this complication to diagnose the cancer in its earliest stage.

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